

Draft

Toxicology Testing Strategy

- Purposes
 - Evaluate Acceptability of Product Changes
 - Evaluate Harm Reduction Efforts

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for the Institute of Medicine Panel Presentation, 3/01/00

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Acceptability Testing vs. Harm Reduction Testing

- Acceptability
 - allow no significant increase in existing activity
 - allow no significant introduction of new activity
- Harm Reduction
 - decrease existing activities

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Philip Morris Guidelines

- Modeled after FDA "Redbook" for the evaluation of food additives
- Covers Evaluation of Ingredients, Processes and Novel Products
- Addresses specific properties of chemicals (e.g. carcinogens)
- Tiered approach to testing
- Reviewed by an external scientific advisory board (SAB)

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International Testing Standards

- OECD (Organization of Economically Developed Countries)
- ICH (International Congress on Harmonization)
- GLP (Good Laboratory Practices)

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Testing Approach

- Relative comparison of activity
 - Test versus an appropriate cigarette control
- Selection of control
 - single change relative to control
 - use of a standard reference cigarette

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Typical Test Design

- Controls
 - Specific to ingredient (cigarette without the ingredient)
 - Assay controls (ex. Sham, positive controls, solvent)
- Tests
 - 1X use level of ingredient
 - 10X use level of ingredient
 - 100X use level of ingredient

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Assay Selection Criteria

- Responsive to smoke
- Able to differentiate among different cigarettes
- Meet typical regulatory standards
- Covers a spectrum of endpoints

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Standard Assays

- Smoke Chemistry
- Genotoxicity
- Cytotoxicity
- Inhalation

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Smoke Chemistry

- List developed from chemicals identified by the CPSC (Consumer Product Safety Commission) and IARC (International Agency for Research on Cancer)
- Analysis of both gas/vapor and particulate phases
- Covers many chemical classes

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Smoke Chemistry

- List of chemicals by class

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Genotoxicity

- *Salmonella* reverse mutation (Ames Test)
 - 5 tester strains
 - +/- S9
 - Test material: particulate phase
- TK Assay in mammalian cells
 - Test material: particulate phase
 - Under validation
- Rat micronucleus
 - Test material: diluted smoke
 - Under validation

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Cytotoxicity

- 3T3 cells
- neutral red uptake
- Test material: particulate phase and gas/vapor phase

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Inhalation Study

- Rats
- 90 day exposure, 6 hr / day, 7 days / week
- Test material: diluted smoke
- Many endpoints evaluated (OECD)
- Focus is on histopathology of the respiratory tract

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Relationship of the Assays

- Complementary battery
- Aldehydes play a role in the cytotoxicity and inhalation assays

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Smoke Collection

- Cigarette conditioning
- Standard conditions
 - FTC (Federal Trade Commission)
 - ISO (International Standards Organization)
- Relative comparison of cigarettes
 - Not meant to mimic human smoking
 - Consistency is important for appropriate comparisons

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Charts from Profile

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Alternate Smoke Machine Profiles

- **Conclusions**
 - Different smoking conditions give different total yields
 - The relative proportions of smoke constituents appear relatively unchanged
- **Plans**
 - Conduct biological assays under alternate smoking machine conditions

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Role of Experimental Results in Harm Reduction

- Possible basis for comparison
 - Cigarette
 - TPM
 - CO
 - nicotine
 - other
- Link to human exposure

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Use of Exposure Data

- Experimental data provide a relative comparison of activity
- Human Data
 - Uptake
 - biomarkers

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Electrically-Heated Cigarette

- Objective
- Technology
- Toxicology testing
- Marketplace experience

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Electrically-Heated Cigarette: Objective

- Reduce biological activity
- Reduce yield of toxic smoke constituents
- Reduce environmental tobacco smoke
- No ashes
- Low odor

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Electrically-Heated Cigarette: Technology

- Goal to reduce burn temperature
- Controlled electric heating of tobacco
- Special cigarette design

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EHC Heater Design

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EHC Cigarette Design

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Electrically-Heated Cigarette: Toxicology Testing

DRAFT

- Smoke chemistry
- Ames Assay
- Cytotoxicity
- Inhalation

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Selection of Control

- 1R4F
 - University of Kentucky reference
 - 9 mg tar delivery
 - representative of the middle of the US market
 - commonly used in cigarette research

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Smoke Chemistry

- Not quantifiable in either EHC or 1R4F

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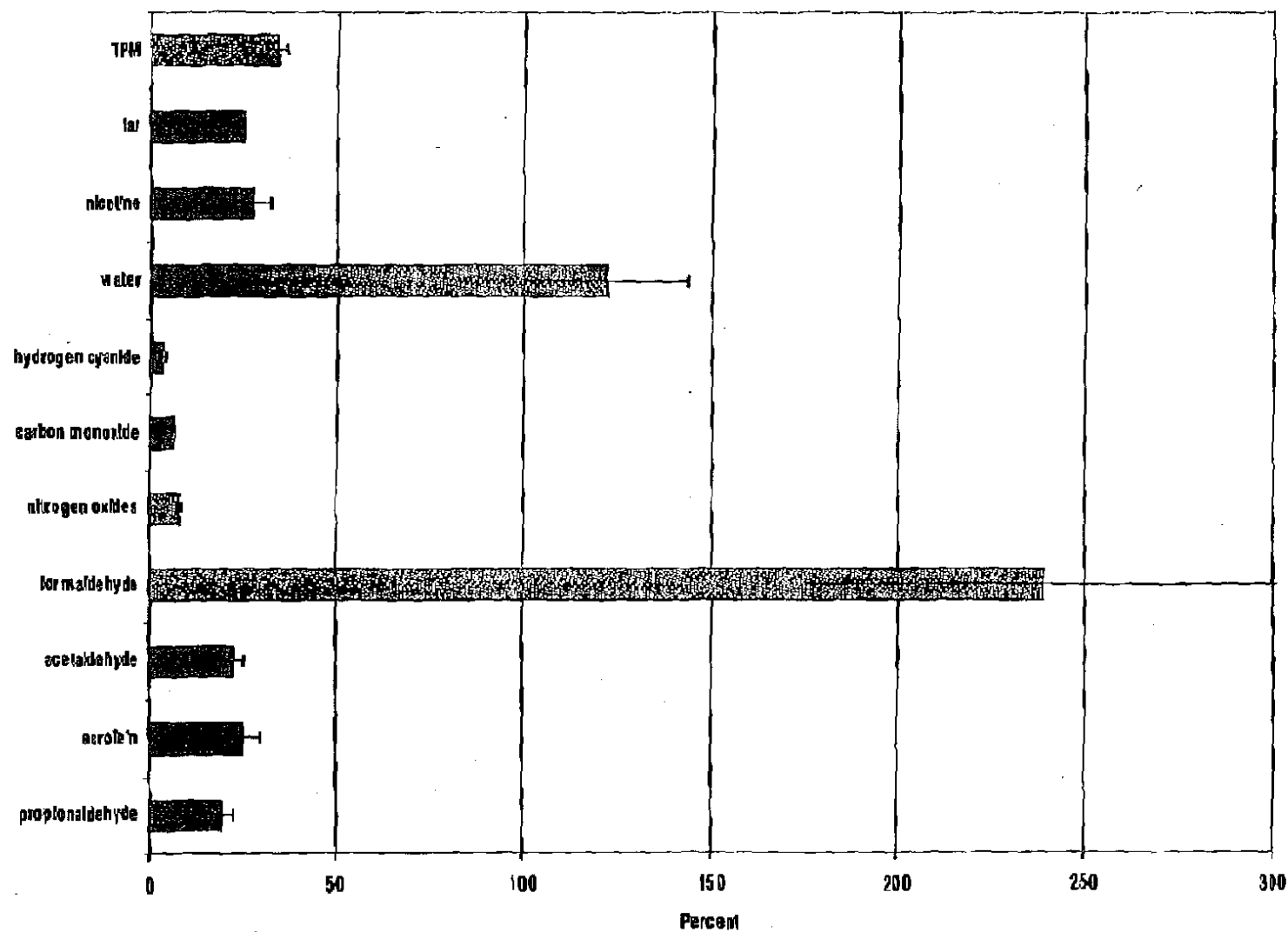
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Smoke Chemistry

(EHC yield per cigarette relative to 1R4F)

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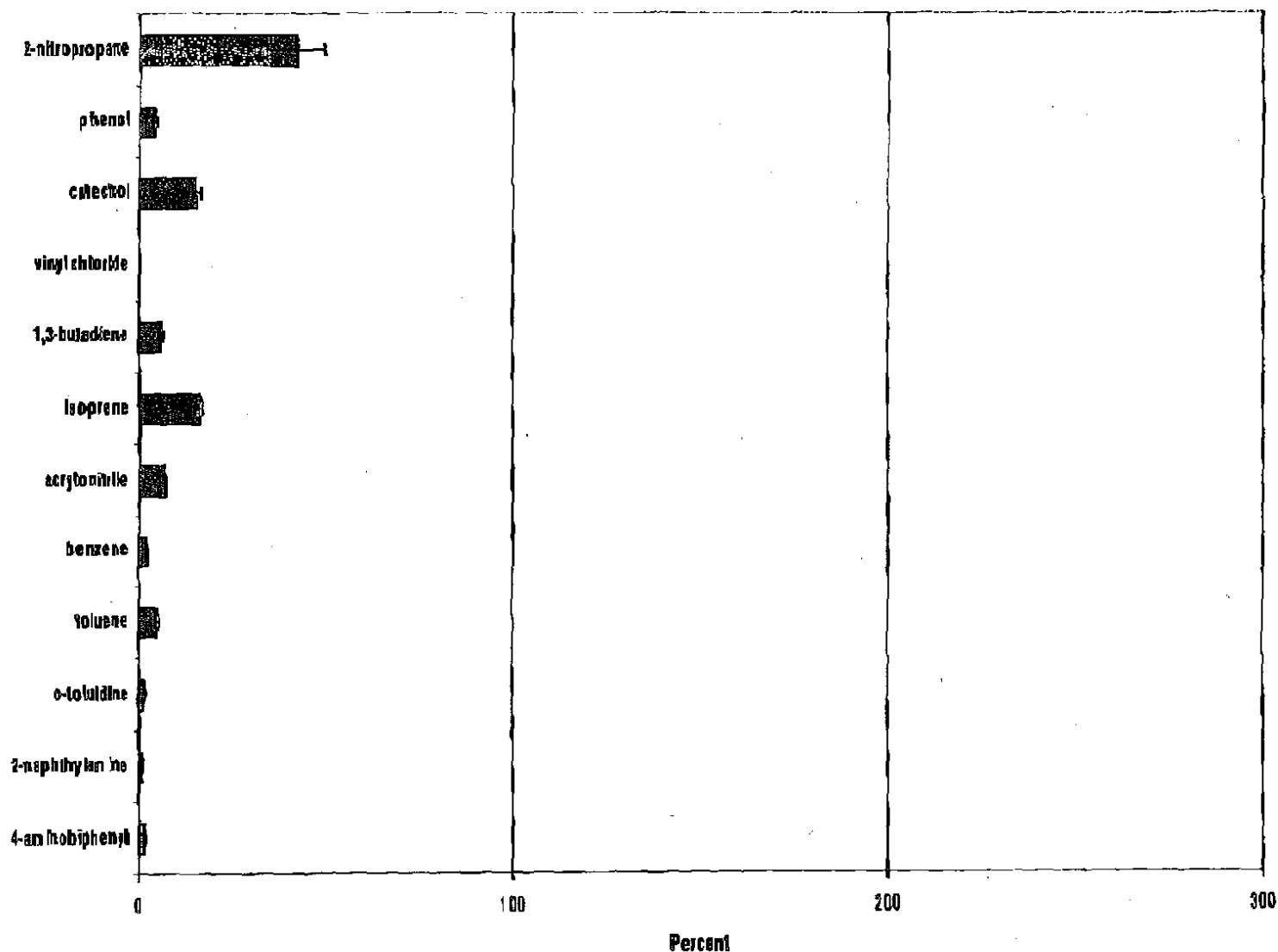
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Smoke Chemistry

(EHC yield per cigarette relative to 1R4F)

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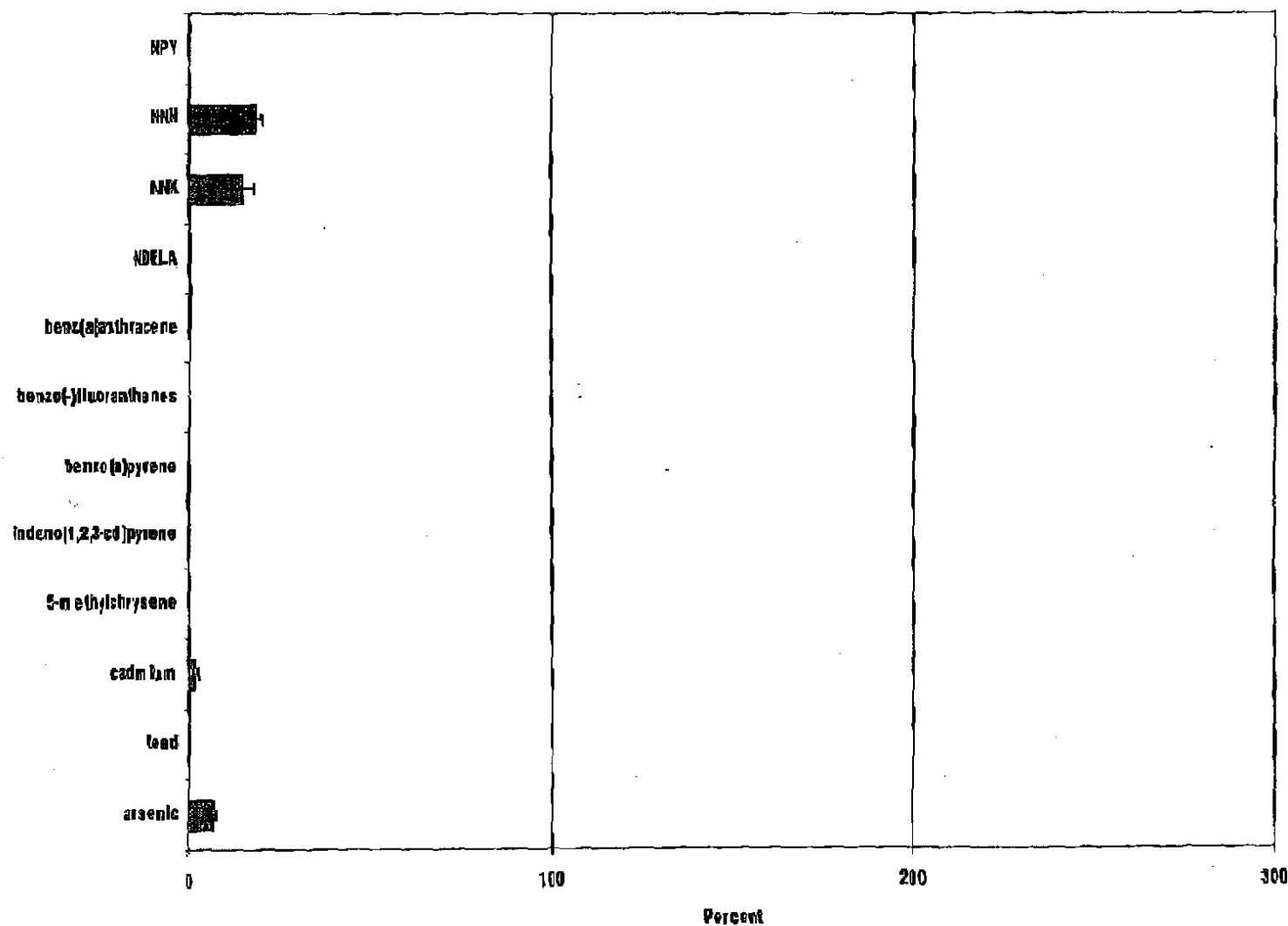
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Smoke Chemistry

(EHC yield per cigarette relative to 1R4F)

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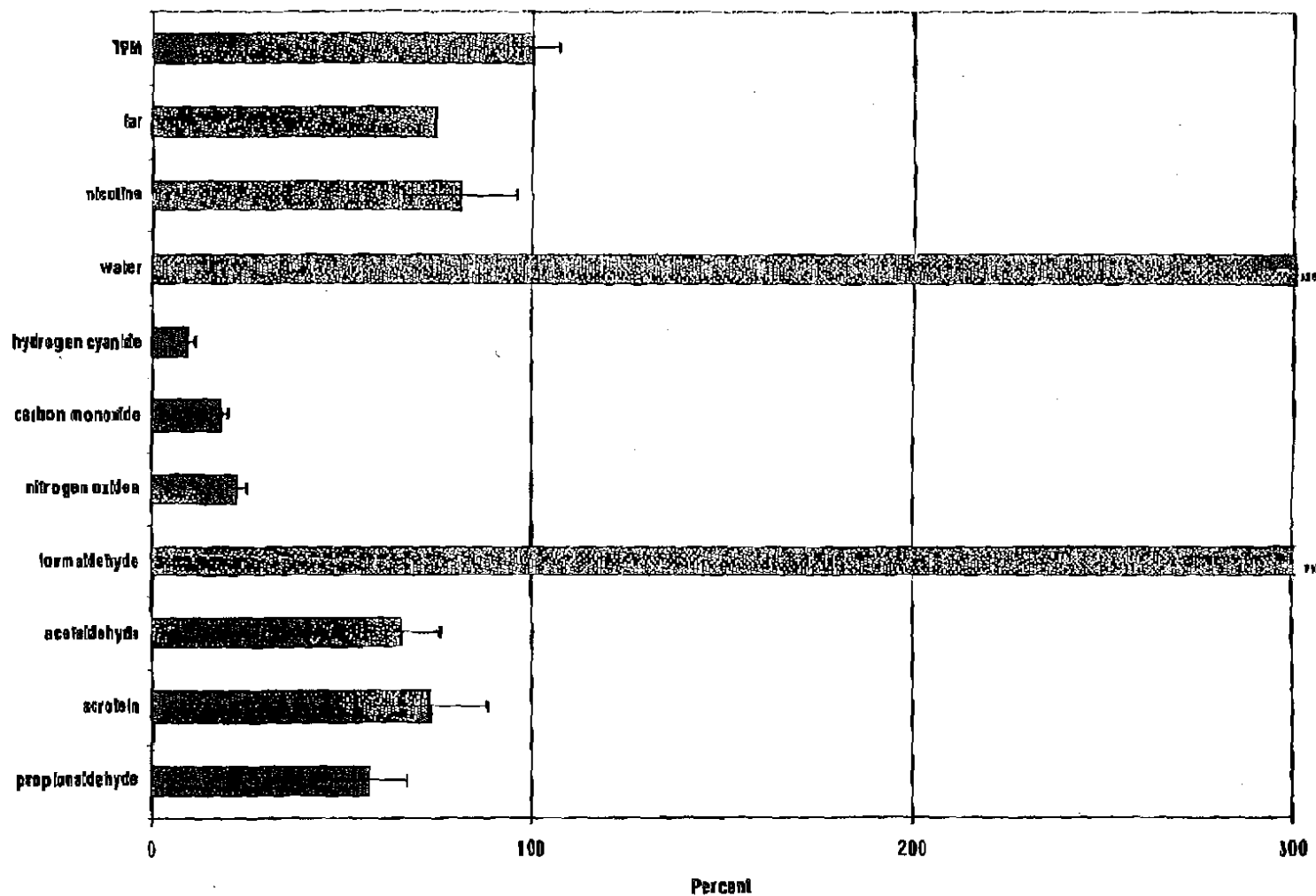
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Smoke Chemistry

(EHC yield per TPM relative to 1R4F)

DRAFT



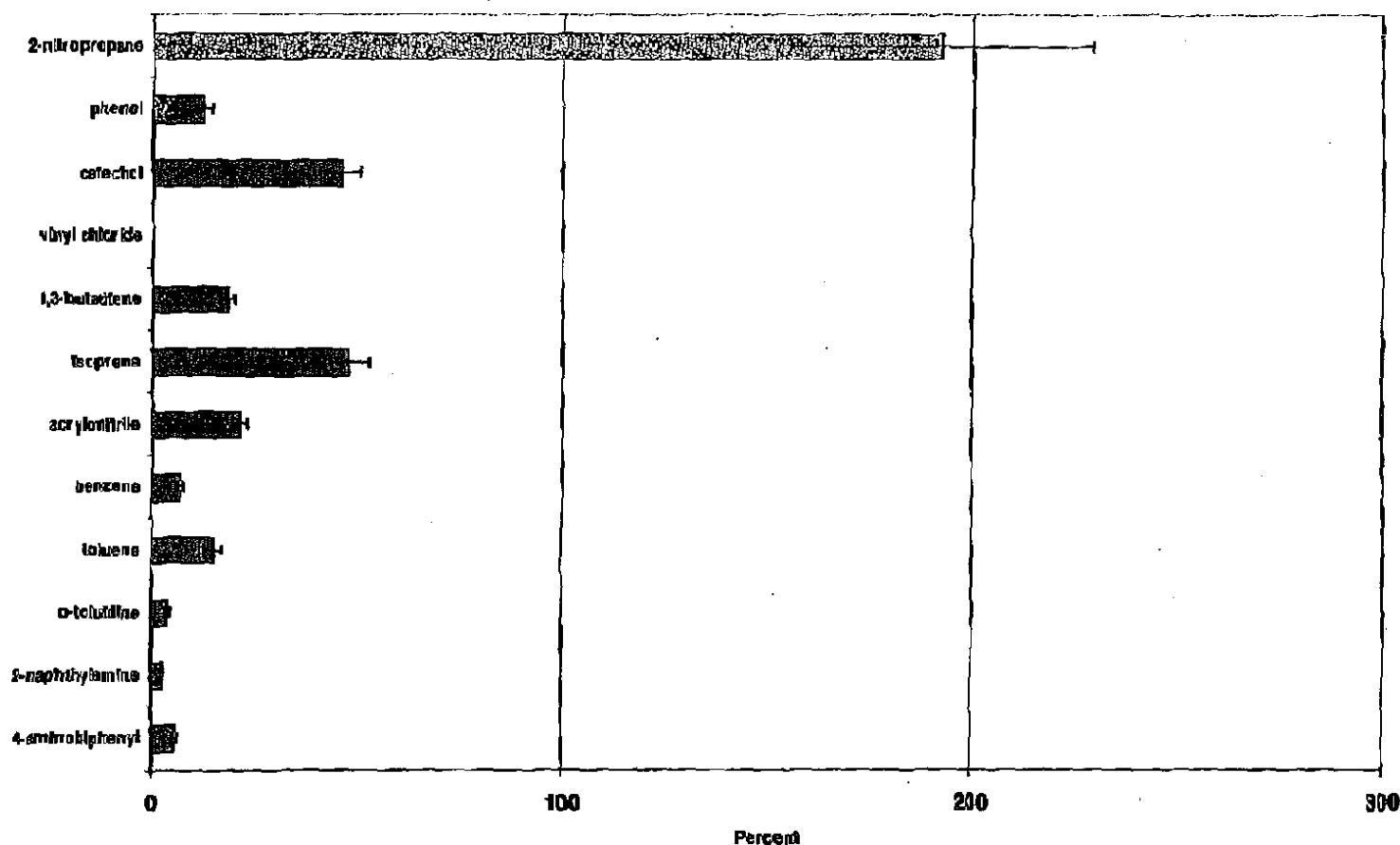
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Smoke Chemistry

(EHC yield per TPM relative to 1R4F)

DRAFT



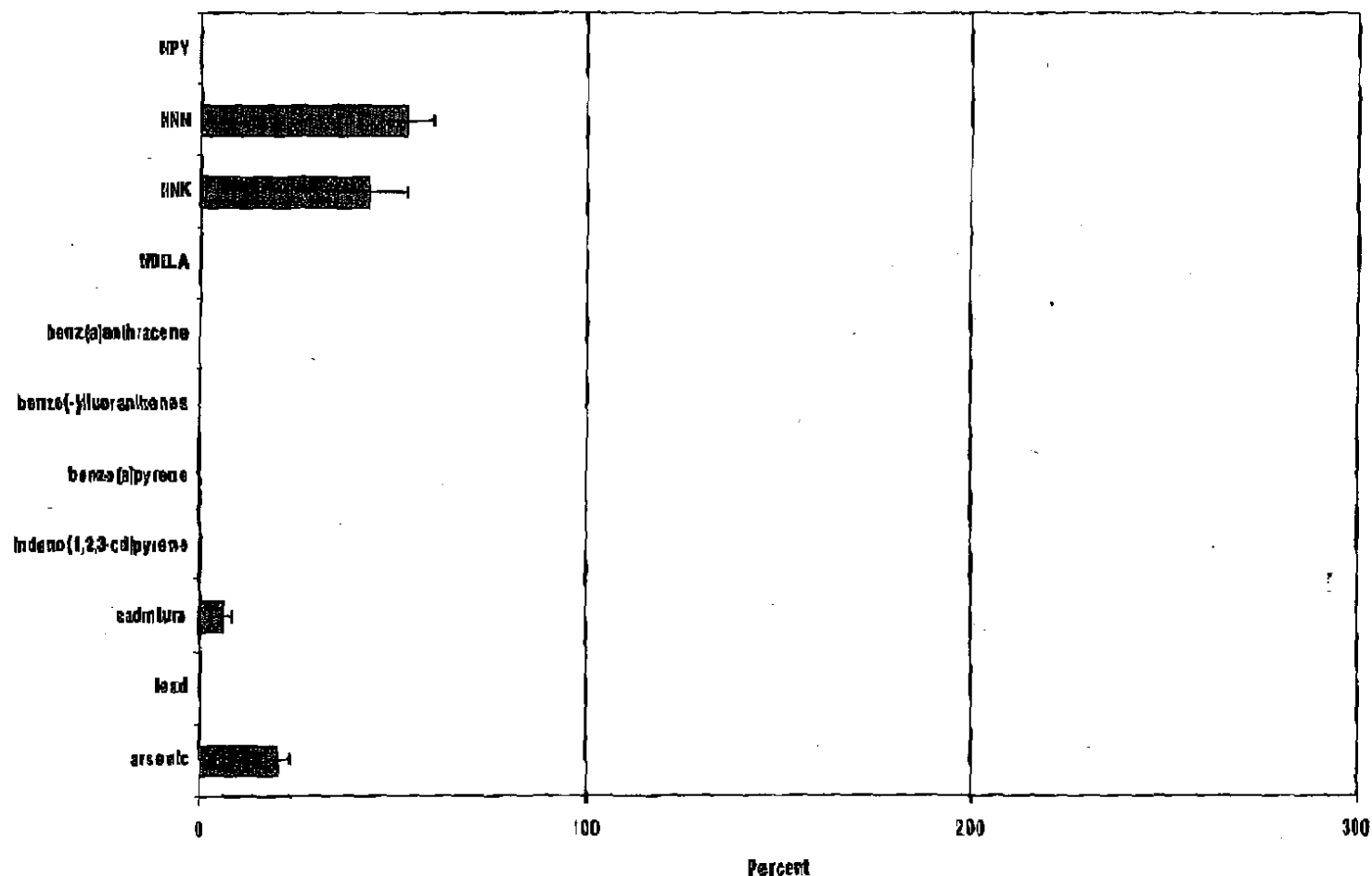
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Smoke Chemistry

(EHC yield per TPM relative to 1R4F)

DRAFT

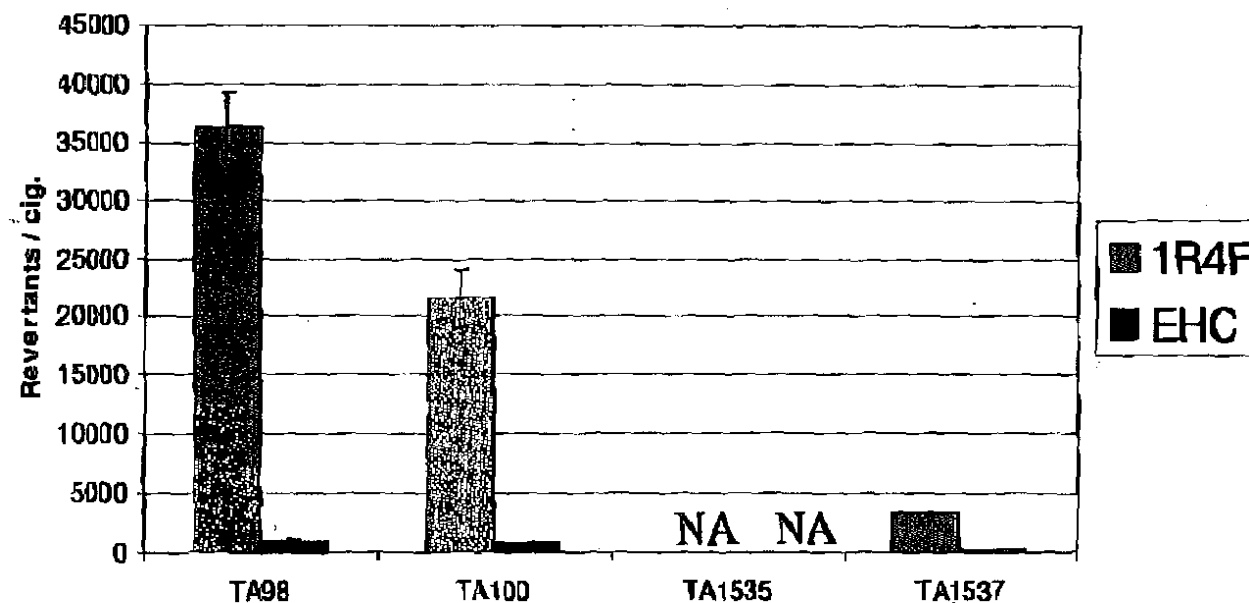


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Ames Assay +S9



NA - Not active

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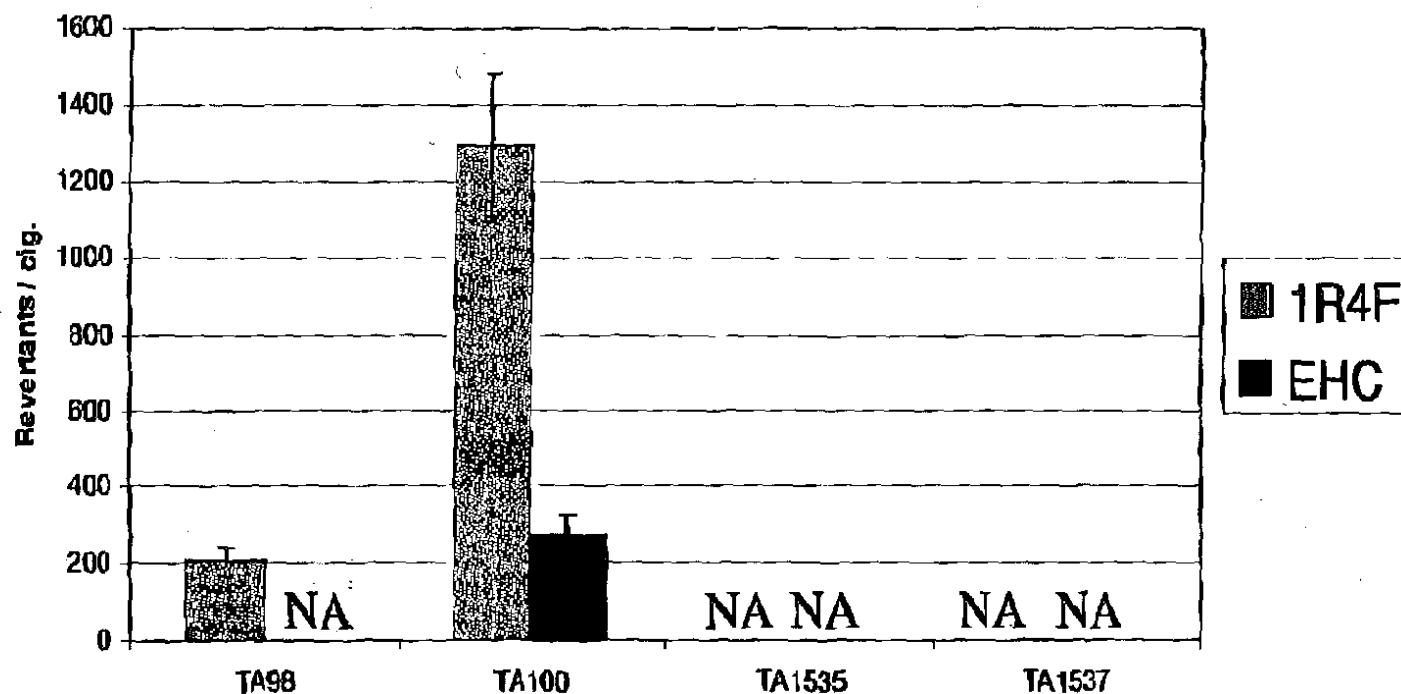
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Ames Assay -S9



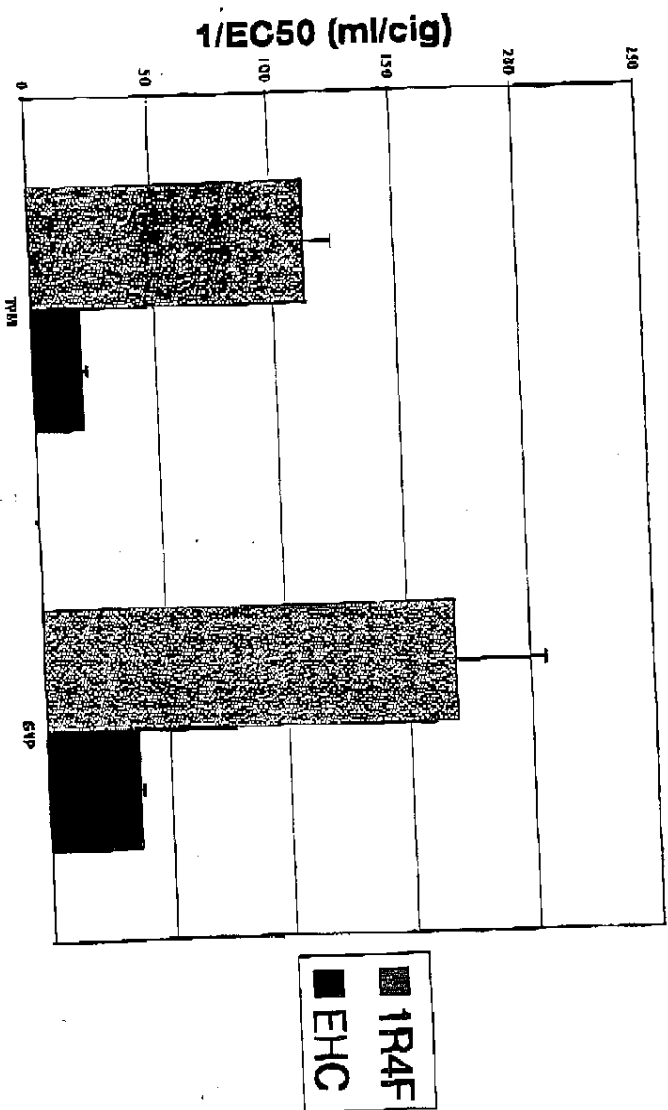
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Cytotoxicity



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DRAFT

Inhalation

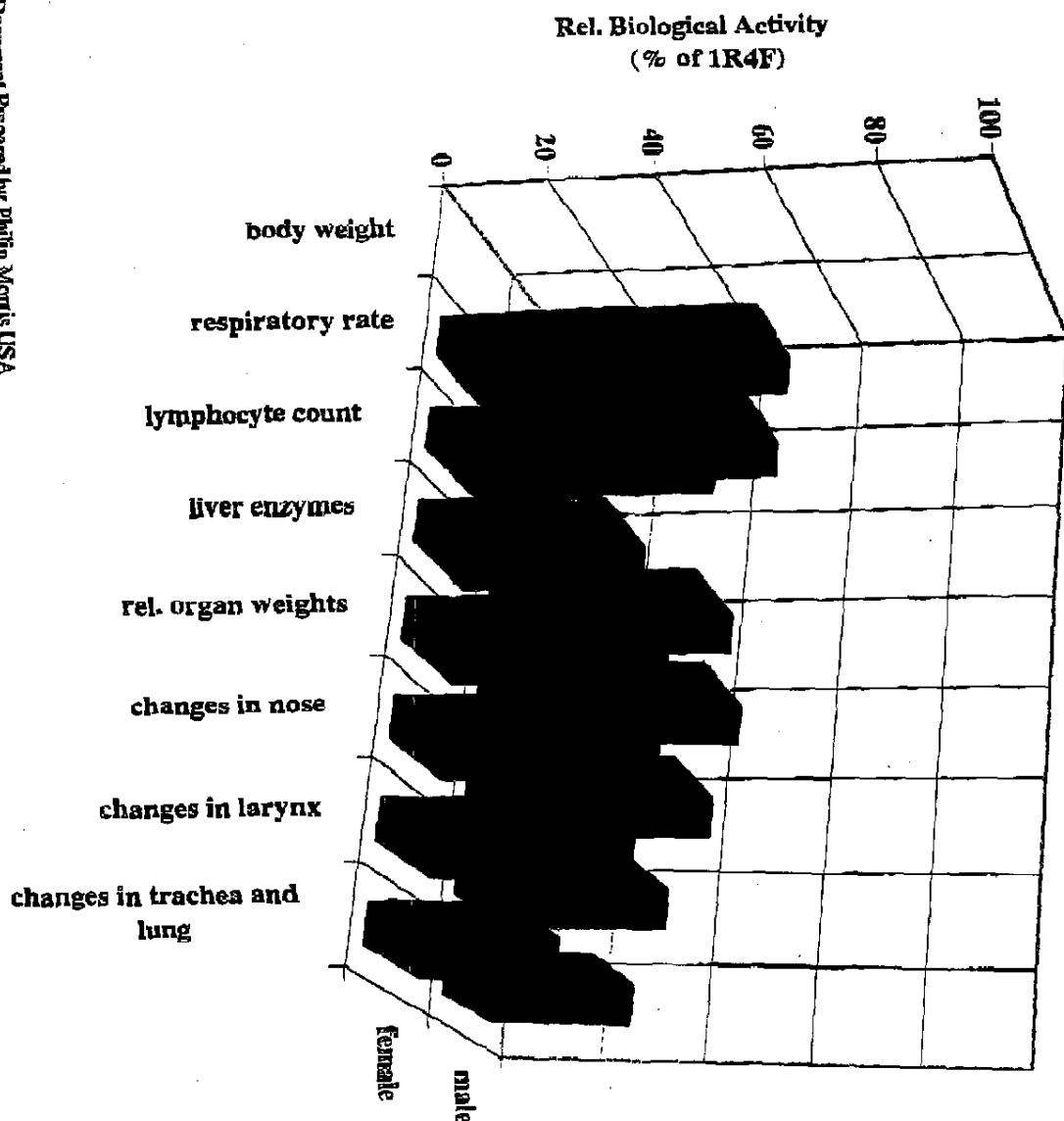
- The effects observed in animals exposed to smoke from the EHC were similar to those typically observed in animals exposed to the smoke from conventional cigarettes, ex. 1R4F.

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Inhalation

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